Thermotolerance and Human Performance: Role of Heat Shock Proteins

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ABSTRACT

Introduction

Thermotolerance (intrinsic and acquired) is the ability of the body and its cellular structures to withstand severe destructive heat stress. Acquired thermotolerance [adaptive] (ATT) is induced by pre-exposure to elevated but non-lethal temperatures and leads to enhanced cellular protection, synthesis of stress and heat shock proteins (HSPs), and reduced risk from subsequent heat injury. Enhanced intrinsic [native] thermotolerance (ITT), which has been described in several non-human organisms (i.e., nematodes, yeast), has been demonstrated when these organisms are subjected to pre-lethal exposure during a variety of developmental stages. Furthermore, it has been suggested that the molecular mechanisms and signalling pathways for ITT and ATT may be different.

Rationale

Given that novel interventions which may lead to enhanced ITT could play a role in human physical performance and adaptability to known lethal environments (i.e., radioactive, excessive heat), characterization of these biological pathways are warranted. The role and signalling pathways of ITT are relatively unknown in humans. Moreover, whether or not subsets of the populations (i.e., East African runners) have greater native or induced thermotolerance remains controversial. It is likely that individual thermoregulatory responses to exercise heat stress are due the combination of ITT and ATT; however, the focus of most studies has been on ATT.

Methods

The question remains "can science and technology be exploited to make man more resistant to environmental stressors? Human's resistance to environmental heat stress by increased ITT could be achieved by either genetic or environmental manipulation during early development. However, the possibilities of such robust molecular manipulations could not be achieved with significant ethical considerations.

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14. ABSTRACT
Thermotolerance (intrinsic and acquired) is the ability of the body and its cellular structures to withstand severe destructive heat stress. Acquired thermotolerance [adaptive] (ATT) is induced by pre-exposure to elevated but non-lethal temperatures and leads to enhanced cellular protection, synthesis of stress and heat shock proteins (HSPs), and reduced risk from subsequent heat injury. Enhanced intrinsic [native] thermotolerance (ITT), which has been described in several non-human organisms (i.e., nematodes, yeast), has been demonstrated when these organisms are subjected to pre-lethal exposure during a variety of developmental stages. Furthermore, it has been suggested that the molecular mechanisms and signalling pathways for ITT and ATT may be different.

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Conclusions

By exploring the molecular mechanisms of ITT in humans, we could begin to understand how to tolerate higher body temperatures, increase physical performance, and reduce the risk of severe heat injury and death.

1.0 PURPOSE

Thermotolerance (intrinsic and acquired) is the ability of the body and its cellular structures to withstand heat stress that exceeds the optimal temperature range of human performance. Acquired adaptive Thermotolerance (ATT) is induced by pre-exposure to non-lethal temperature elevations and leads to enhanced cellular protection, synthesis of heat shock proteins (HSPs), and reduced risk from subsequent heat-induced injury. Enhanced intrinsic Thermotolerance (ITT), which has been described in several non-human organisms (i.e., nematodes, yeast), has been demonstrated when organisms are subjected to pre-lethal exposure during developmental stages. It has been suggested that the molecular mechanisms for ITT and ATT Thermotolerance may be different. The question remains whether or not thermotolerance can be modulated by low level stresses such as exercise or heat stress during early developmental stages? This review will discuss how organisms have naturally evolved stress response networks and how these developed networks could potentially be manipulated by heat stress, exercise, and other mechanism to modulate thermotolerance and heat shock mechanisms. In addition, the relationship of the adaptation to heat shock and longevity of organisms will be explored. The advancement of science and technology underlying the physiological aging process which involved stress proteins (i.e., heat shock) has the potential not only to extend natural life spans, but also simultaneously to postpone many of patho-physiological states.

2.0 OVERVIEW OF THERMAL TOLERANCE

Thermal Tolerance refers to cellular changes from a severe non-lethal heat exposure that allows the organism to survive a subsequent and otherwise lethal heat exposure. Thermal Tolerance and heat acclimation are complementary; acclimation reduces the adverse effects of heat on physiology, whereas Thermal Tolerance increases survivability to a given heat load. Thermal Tolerance is associated with the production of specialized proteins that bind to various molecules to provide cellular protection and to accelerate tissue repair. In addition to the actions of heat shock proteins, other pathways and cellular systems likely contribute to Thermal Tolerance Thermotolerance is an increased resistance of cells, tissues, and organisms to elevated temperatures following a prior exposure to heat.

Thermotolerance has been demonstrated in cell lines, tissue culture, and in several animal species. Thermotolerant cells induce the overexpression of a family of Hsps and are thereby protected from cell death caused by various stresses **(Figure 1).** This suggests that the chaperonic function of Hsps is associated with the development of thermotolerance. However, the details of the molecular events underlying heat shock responses are not well defined.

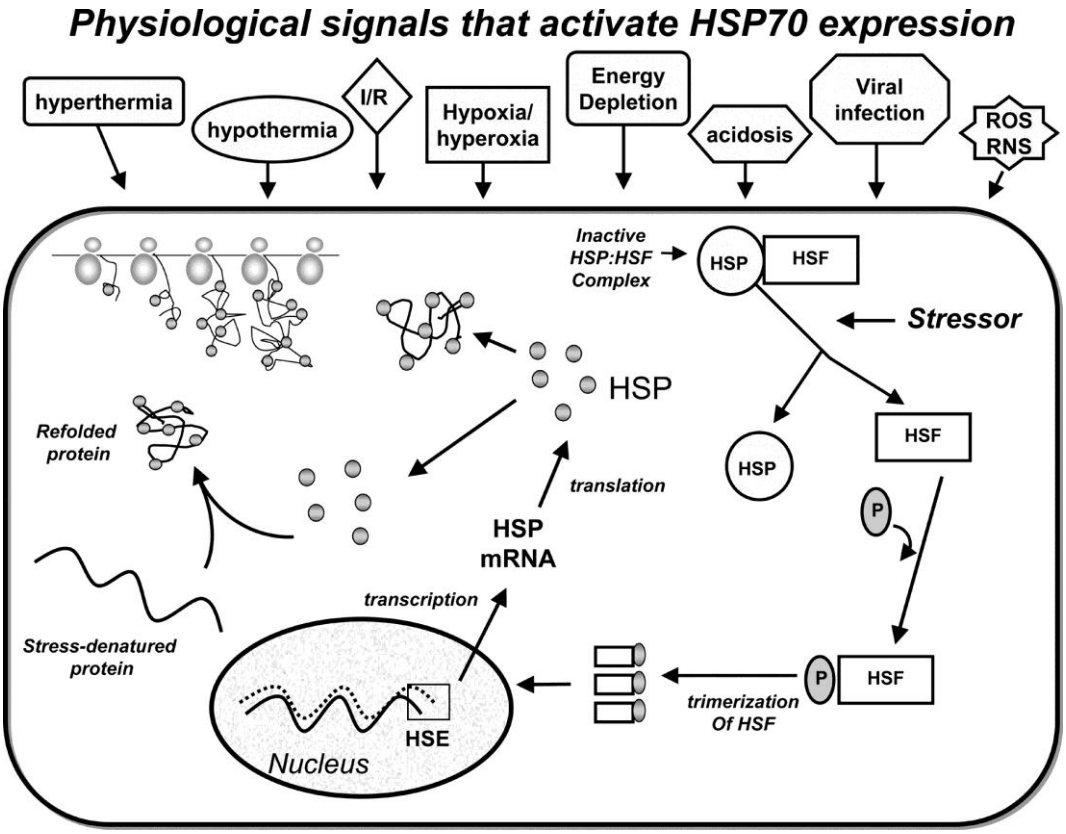

Figure 1: Physiological signals that activate HSP70 expression.

In nature, the majority of organisms are exposed continually to variable ambient temperature conditions and as a result have adapted a robust stress response network which encompasses Hsps that are activated during conditions of pathophysiological stress. HSPs are constituents of this response and typically function as molecular chaperones, which assist in maintaining cellular protein structure. During heat stress, members of the Hsp70 family mitigate cellular damage in many organisms including humans and *Drosophila* (Georgopoulis and Welch, 1993). Heat shock cognate (HSC) 70 and Hsp 70 are the most abundantly expressed members of this family, and both have been implicated in tolerance to hyperthermia. HSC70 is expressed constitutively and is linked to basal thermotolerance, whereas the expression of Hsp70 is heat-induced and is linked to acquired thermotolerance (Georgopoulis and Welch, 1993).

3.0 ROLE OF HEAT SHOCK PROTEINS DURING EARLY DEVELOPMENT

Excessive heat shock is one of the significant teratogens in humans, animals, and insects. However, protection from teratogenic effects as is true for various aspects of the stress response, can be achieved with mild pretreatment and Hsp responses correlate with this tolerance. In the developing embryo, the heat shock response is regulated and has been shown to be involved in the differential response of mammalian brain, germ cells, and specialized somatic cell types. However, whether or not the heat shock response and associated pathways could be regulated in a matter to enhance protection against subsequent heat or other stressors without any negative impacts in the developing embryos is largely unknown. Significant research has focused on the role, induction, and mechanisms of Hsps during developmental stages. Exposure to moderate

to severe temperatures can induce synthesis of Hsp70. Induction of Hsp70 at high temperatures has been shown to adversely impact development and reduce reproductive capacity. In *D. melanogaster*, Hsp70 induction is implicated in reduced fecundity, and Hsp70 overexpression is associated with increased larval mortality (Krebs et al, 1994), retarded growth, and reduced egg hatching (Krebs, 1991). While these findings demonstrate the adverse effects of Hsp70 expression in *D. melanogaster*, beneficial effects of thermotolerance due to Hsp70 induction are also well-established. In heat-acclimated worms after being grown at 25 degrees Celsius, survival is significantly enhanced when compared to worms grown at 20 degrees Celsius during subjection to heat stress (35°C) **(Figure 2).** Therefore, the potential beneficial effects of stress proteins on thermotolerance when compared to any negative effects appear to be largely due to the timing, duration of stress exposure (i.e., heat, metabolic), and the species studied. More work is necessary to better understand if employing titrated heat shock during embryonic development is feasible as an instrument to confer better thermotolerance.

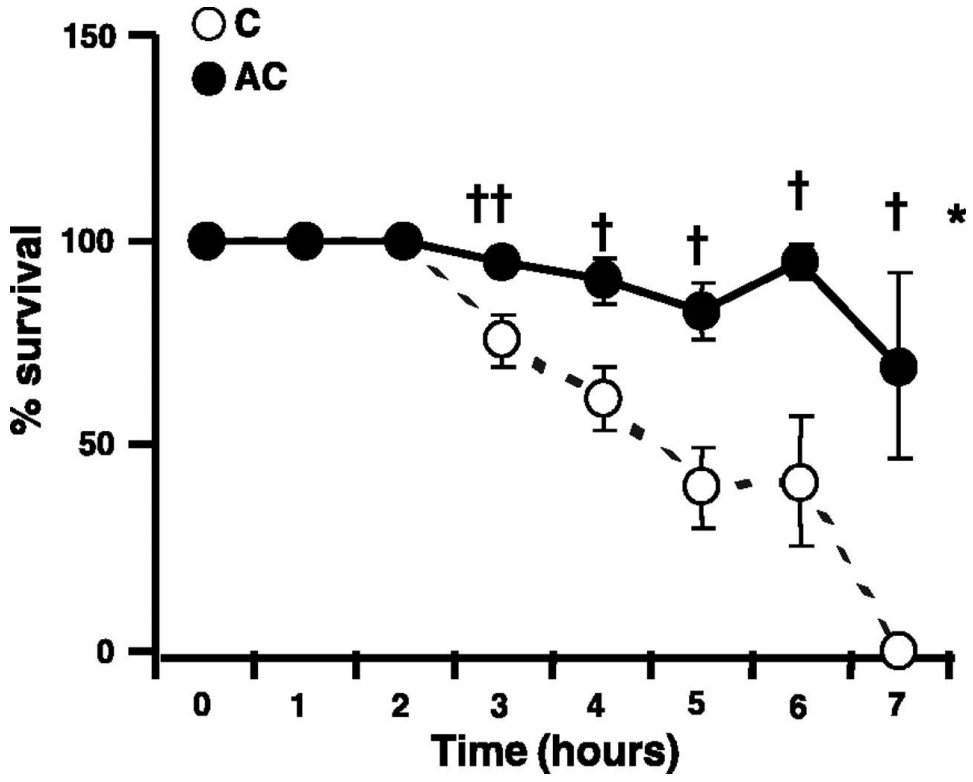

Figure 2: The heat-acclimated C. elegans phenotype: survival curves of adult wild-type worms grown at 20{degrees}C (control, C) and worms grown at 25{degrees}C, AC) during subjection to heat stress at 35{degrees}C. AC worms endured heat stress markedly better than control worms. Treinin, M. et al. Physiol. Genomics 14: 17-24 2003.

3.1 Can Exercise with Associated Heat Stress Confer Better Thermotolerance?

Developing mammalian temperature regulation is dependent on maternal temperature, metabolism, and uterine blood flow (Linddgvist et al, 2003). The maternal uterine environment establishes an ambient temperature, and excess fetal heat is dissipated through a fetal/maternal temperature gradient (Lotgering et al, 1983). During exercise, an increased maternal core temperature may compromise or possibly reverse this

gradient (Lotgering et al, 1983). In effect, the developing fetus may become a partial recipient of the thermal energy generated during maternal exercise.

In the rat, a maternal body core temperature increase of 2.5°C was established as a threshold after which 9.5-day-old fetal rats developed abnormally (Germain et al 1985). The duration of the exposure required to induce fetal malformations declined as temperatures increased above this threshold. Temperature-induced fetal defects have been experimentally produced in chickens, rats, hamsters, guinea pigs, rabbits, sheep, pigs, and monkeys (Edwards et al 2003). However, the type and severity of the fetal defects were dependent upon the species, stage of development, and intensity of the heat stressor.

Without doubt the fetus is dependent upon the uterine environment for life, however, a certain level of autonomy is retained by the fetus. For example, Hsps may be important as a fetoprotective mechanism (Bae et al 2003). It remains unclear whether a chronic maternal exercise program alters the maternal/ fetal heat gradient to a degree that would induce a fetal Hsp response, especially in humans working at 60–70% aerobic capacity ($\dot{V}O_{2max}$). Results from one animal study indicate that maternal core temperature did not reach the threshold that would induce either gross fetal abnormalities or a fetal heat shock protein response (Mottola et al, 2007). Therefore, it remains unknown whether or not maternal heat stress (passive or active) exposure plays a role in the thermal tolerance of offspring.

4.0 ADAPTATION TO STRESS AND LONGEVITY

Some technologies inherent in the extension of health and life span could find applications in the military framework. Currently, clinical developments of therapeutics that slow aging by mimicking caloric restriction are being explored. Interesting, caloric restriction evokes generic heat shock and stress proteins, suggesting that aging and stress related responses share many common molecular pathways. Recently, acute low level bouts of stress (i.e., caloric restriction, heat stress) has been demonstrated to elicit induction of Hsps and other stress genes, which may be beneficial for improving longevity. During sub-lethal stress levels, cells may attempt to survive and activate a stress response system that includes a rapid induction of Hsps. It appears that the developed resistance to stress is often related to longevity. Some scientists have advanced the hypothesis that the stress response may also counteract the negative effects of aging, and that exposing organisms to a mild, sublethal stress, inducing a stress response, may help them to live longer and improve survivability during traumatic injury including heat stroke. However, whether or not these mechanisms affect longevity in humans is currently under investigation. Several mild stresses have been reported to increase longevity (irradiation, heat and cold shock, hypergravity, exercise, etc.), and one of them, hypergravity, to decrease the rate of behavioral aging. Exposure to mild heat-stress (heat-shock) can significantly increase the life expectancy of the nematode Caenorhabditis elegans. More than 40 single-gene mutants in Caenorhabditis elegans have been demonstrated to lead to increased lifespan (a rigorous, operational test for being a gerontogene) and A single heat-shock early in life extends longevity by 20% or more (Wu et al, 2009). Repeated mild heat-shocks throughout life have a larger effect on life span than does a single heat-shock early in life. In mammals, both dietary restriction and hormesis are phenomena in which the endogenous level of resistance to stress has been upregulated; both of these interventions extend longevity, suggesting possible evolutionary conservation. Recently, Westerheide and colleagues showed that human heat shock factor (HSF)1 is inducible at a critical residue that negatively regulates DNA binding activity and provide a mechanistic basis for the requirement of HSF1 in the regulation of life span and establish a role for SIRT1 in protein homeostasis and the HSR (Westerheide et al, 2009). The mechanisms whereby these stresses increase longevity have not yet been elucidated.

5.0 SUMMARY

Thermal Tolerance refers to cellular changes from a severe non-lethal heat exposure that allows the organism to survive a subsequent and otherwise lethal heat exposure. Thermal Tolerance and heat acclimation are complementary; acclimation reduces the adverse effects of heat on physiology, whereas Thermal Tolerance increases survivability to a given heat load. Thermal Tolerance is associated with the production of specialized proteins that bind to various molecules to provide cellular protection and to accelerate tissue repair.

Organisms have naturally evolved stress response networks that could be potentially manipulated by heat stress, exercise, and other mechanism to modulate thermotolerance and heat shock mechanisms. Thermotolerance is an increased resistance of cells, tissues, and organisms to elevated temperatures following a prior exposure to heat. It remains unknown whether or not maternal heat stress (passive or active) exposure plays a role in the thermal tolerance of offspring.

The relationship of the adaptation to heat shock and longevity of organisms could have significant implications for combating the negative impacts of stress (i.e., heat stroke, combat stress) associated with being a Soldier. Acute low level bouts of stress (i.e., caloric restriction, heat stress) has been demonstrated to elicit induction of Hsps and other stress genes, which may be beneficial for improving longevity. In the near term, identification of key longevity genes, development of anti-aging therapeutics, caloric-restriction strategies, and others may be key in understanding the relationships of DNA repair mechanisms and "enhanced stress tolerance" leading to enhanced thermal tolerance and human performance.

> The views expressed in this paper are those of the authors and may not necessarily be endorsed by the U.S. Army.

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